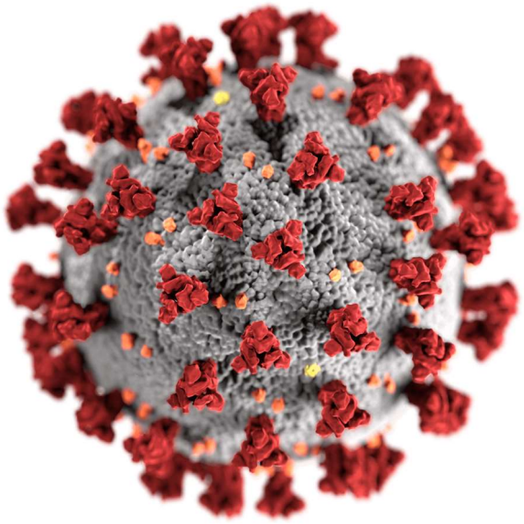


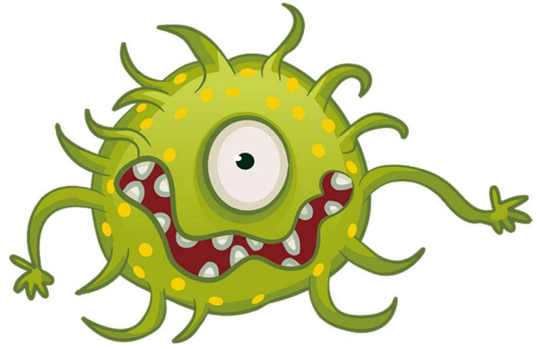
COVID-19

A highlight on The Management Protocol and Potential Treatments

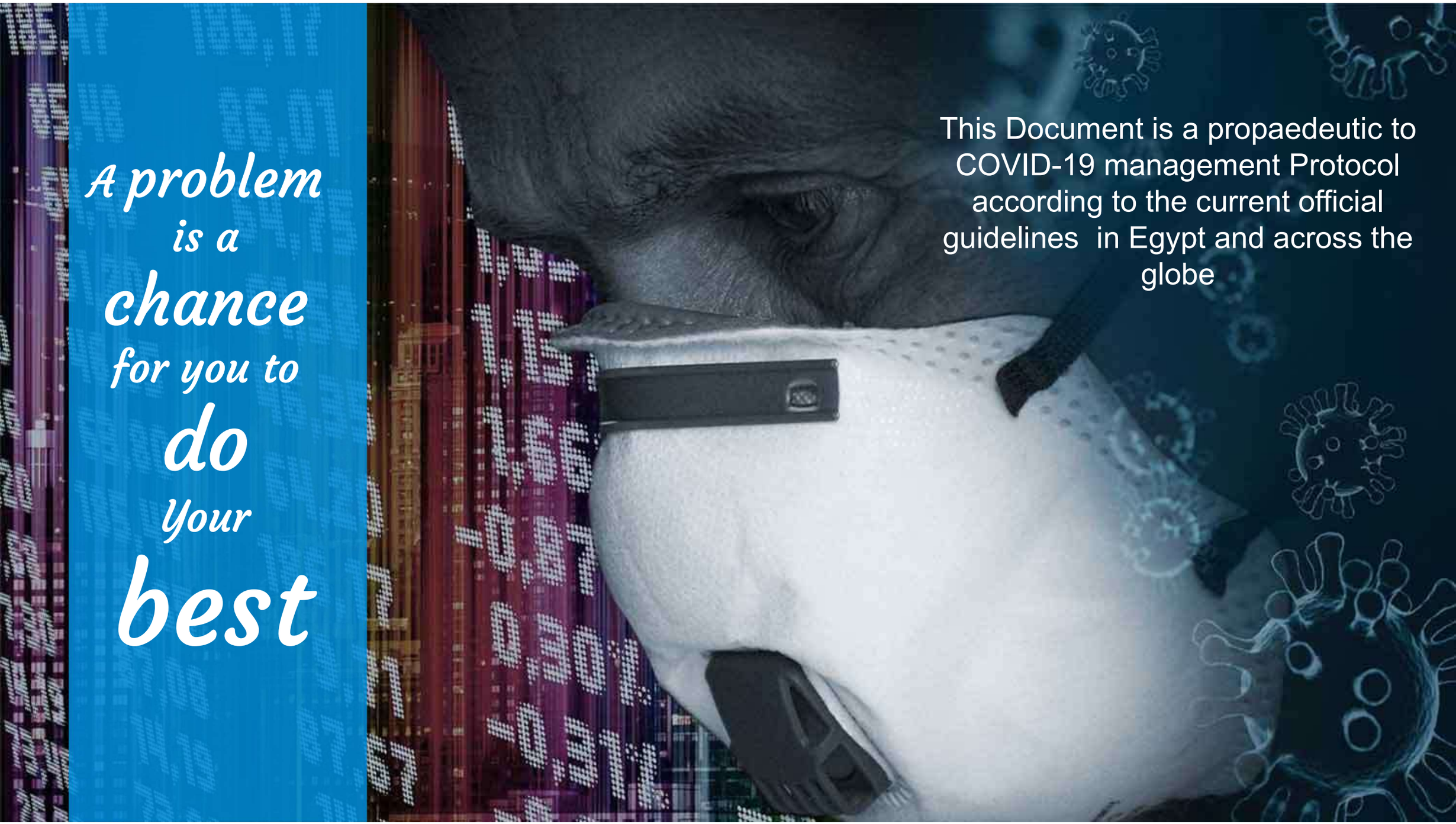
Cairo University Hospitals

Drug Information Center

K.D.I.C



A problem is a chance for you to do Your best

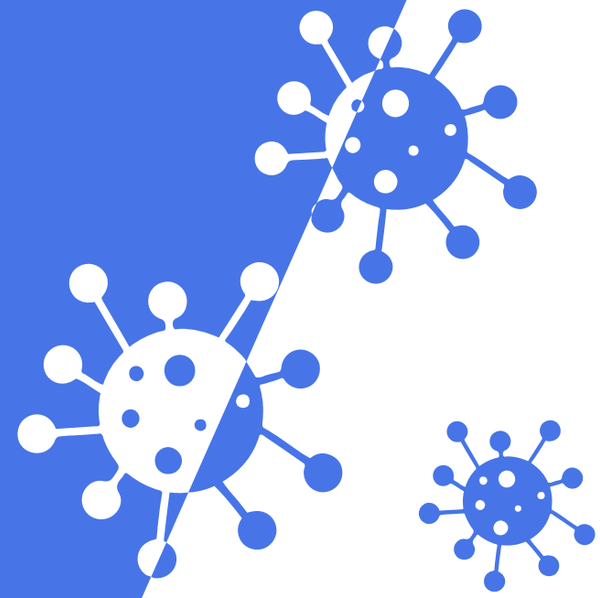


This Document is a propaedeutic to COVID-19 management Protocol according to the current official guidelines in Egypt and across the globe

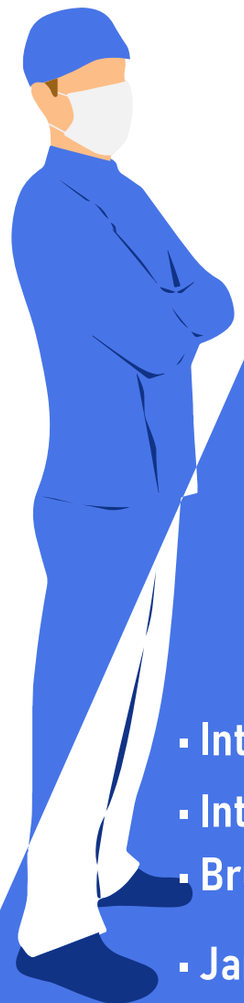
EDITORIAL BOARD

Editor-in-chief
Dr.Doaa Al Asy
Head of KDIC

Editors
Dr. Omar Tohamy
Dr. Islam Omar
Dr. Ahmed A.Hassan



Disclaimer



This document contains all the potential drugs for management of COVID-19 Patients as follows

Drugs available in Egypt:

- Chloroquine, Hydroxy Chloroquine.
- Azithromycin + Chloroquine
- Remdesivir.
- Interferons (alfa or beta).
- Tocilizumab, Baricitinib , Ivermctin.
- Convalescent plasma.
- Corticosteroids; Dexamethasone.
- Ibrutinib.

Drugs Not available in Egypt:

- Interleukin-1 inhibitors (e.g., anakinra).
- Interleukin-6 inhibitors (e.g., sarilumab, siltuximab).
- Bruton's tyrosine kinase inhibitors (e.g., acalabrutinib, zanubrutinib)
- Janus kinase inhibitors (e.g. ruxolitinib, tofacitinib).
- Bamlanivimab.

INDEX

- Epidemiology ……..…….. 6
- Clinical Presentation ……..……7
- Routes of Transmission……...…….....11
- Testing ……...…..…....12
- Virology testing ……..……....13
- Serologic testing ……..…….....14
- Prevention and Prophylaxis ……..…… 16
- The MOH Protocol…….. 21
- Treatment approaches ……..…. 25
- Management of hospitalized patients ……..…… 61
- Special consideration for pregnancy..……..…….. 65
- Special considerations for HIV Patients…..... 67
- Vitamin C ……...…69
- Vitamin D ……... 70
- Zinc ……....71
- Considerations for certain concomitant medications …... 72
- Other ICU related complications ……..…..... 73
- Influenza and COVID-19……74
- Emergency Use Authorization of Bamlanivimab ……...76
- References ……...80

Epidemiology

- The COVID-19 pandemic has exploded since cases were first reported in China in December 2019.
- Individuals of all ages are at risk for infection and severe disease. However, the probability of serious COVID-19 disease is higher in people aged ≥60 years, those living in a nursing home or long-term care facility, and those with chronic medical conditions.
- **Recently, SARS-CoV-2 has been associated with a potentially severe inflammatory syndrome in children (multisystem inflammatory syndrome in children or MISC).**

Clinical Presentation[1]

COVID-19 Pandemic

- The estimated incubation period for COVID-19 is up to 14 days from the time of exposure, with a median incubation period of 4 to 5 days.
- The spectrum of illness can range from asymptomatic infection to severe pneumonia with acute respiratory distress syndrome (ARDS) and death.
- The abnormalities seen in chest X-rays vary, but bilateral multi-focal opacities are the most common.

- Common laboratory findings of COVID-19 include leukopenia and lymphopenia. Other laboratory abnormalities have included elevated levels of aminotransferase, C-reactive protein, D-dimer, ferritin, and lactate dehydrogenase.
- While COVID-19 is primarily a pulmonary disease, emerging data suggest that it also leads to cardiac, dermatologic, hematological, hepatic, neurological, renal and other complications.

Dermatologic manifestations and complications of COVID-19

One early study found that only 2 of 1099 patients had a “rash”, but investigators may have missed several patients. A more recent study found rash occurred in 18 of 88 patients, with 8 of these patients having rash at onset, while another study found that rash occurred in 5 out of 103 patients

A rash associated with COVID-19 can involve various body regions, most commonly the trunk, but extremity involvement may also occur. Pruritus is often minimal but depends on the type of rash, and lesions typically heal quickly, appearing within 3 days and disappearing within 8 days

Patients with COVID-19 most commonly present with respiratory symptoms, but multiorgan involvement can occur, with multiple skin manifestations. *Dermatologic findings* may include a maculopapular rash, urticaria, vesicular rash, petechia, purpura, chilblains, livedo racemosa, and distal ischemia. These rashes should trigger consideration of COVID-19, and understanding these manifestations is important to help identify potential COVID-19 patients and properly treat complications.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7274995/

Gastrointestinal symptoms common in COVID-19 patients

A study found that a third of the people with mild COVID-19 had **diarrhea**. The problem, including watery stool, was usually not severe. The diarrhea lasted for an average of 5 days.

Those with digestive symptoms were more likely to have a **positive stool test** for the coronavirus, which means they had SARS-CoV-2 RNA in their poop. It also took them ***longer to clear the virus*** from their bodies, compared to those without gastrointestinal symptoms.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7438210/

Persistent Symptoms or Illnesses After Recovery from Acute COVID-19

Some of the persistent symptoms that have been reported include **fatigue, joint pain, chest pain, palpitations, shortness of breath, and worsened quality of life**. One study from China found that pulmonary function was still impaired 1 month after hospital discharge. A study from the United Kingdom reported that among 100 hospitalized patients (32 received care in the ICU and 68 received care in hospital wards only), 72% of the ICU patients and 60% of the ward patients experienced fatigue and breathlessness at 4 to 8 weeks after hospital discharge.

Neurologic and psychiatric symptoms have also been reported among patients who have recovered from acute COVID-19. High rates of **anxiety** and **depression** have been reported in some patients using self-report scales for psychiatric distress. Younger patients have been reported to experience more psychiatric symptoms than patients aged >60 years.

Patients may continue to experience **headaches**, vision changes, hearing loss, loss of taste or smell, impaired mobility, numbness in extremities, tremors, myalgia, memory loss, cognitive impairment, and **mood changes for up to 3 months** after diagnosis of COVID-19.

https://pubmed.ncbi.nlm.nih.gov/32729939/ https://pubmed.ncbi.nlm.nih.gov/32753338/

Routes Of Transmission

Transmission of SARS-CoV-2 occurs primarily through respiratory secretions, and, to a lesser extent, contact with contaminated surfaces.

Most transmissions are thought to occur through droplets.[2]

Corona Virus testing

The COVID-19 Treatment Guidelines Panel (the Panel) **recommends** that a molecular or antigen test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) should be used to diagnose acute SARS-CoV-2 infection **(AIII)**.[2]

TYPES OF TESTING

1. **Virology** testing
2. **Serologic** (Antibody) Testing
3. The optimal pulmonary **imaging** technique for people with COVID-19 is yet to be defined, Initial evaluation may include chest x-ray, ultrasound, or if indicated, computerized tomography (CT). Electrocardiogram (ECG) should be performed if indicated.[3]

Virology Testing

Virology testing (i.e., using a molecular diagnostic or antigen test to detect

SARS-CoV-2) should be done in all persons with a syndrome consistent with COVID-19

While initial diagnostic tests for SARS-CoV-2 infection have relied on reverse transcriptase polymerase chain reaction platforms

The CDC recommends that nasopharynx samples be used to detect SARS-CoV-2. Nasal swabs or oropharyngeal swabs are acceptable alternatives.

. Although lower respiratory tract samples have a higher yield than upper tract samples, they are often not obtained because of concerns about aerosolization of virus during sample collection procedures.

The following are the current CDC priorities for COVID-19 diagnostic testing:

High Priority:

- Hospitalized patients **with symptoms**
- Health care facility workers, workers in congregate living settings, and first responders **with symptoms**
- Residents in long-term care facilities or other congregate living settings, including prisons and shelters, with symptoms.

Priority:

- Persons **with symptoms** of potential COVID-19 infection, including fever, cough, shortness of breath, chills, muscle pain, new loss of taste or smell, vomiting or diarrhea, and/or sore throat.
- Persons **without symptoms** who are prioritized by health departments or clinicians, for any reason, including but not limited to public health monitoring, sentinel surveillance, or screening of other asymptomatic individuals according to state and local plans.

Serologic (Antibody) Testing

Given that molecular diagnostic tests and antigen tests for SARS-CoV-2 occasionally yield false-negative results, in some settings, serologic tests have been used as an additional diagnostic test in patients strongly suspected to have SARS-CoV-2 infection.

The Panel does not recommend the use of serologic testing as the sole basis for diagnosing acute SARS-CoV-2 infection **(AIII) ; because** it may take 21 days or longer after symptom onset for seroconversion or detection of immunoglobulin M and/or immunoglobulin G antibodies to SARS-CoV-2.

Possible Cross-reactivity between dengue virus & SARS-CoV-2 which can lead to false-positive dengue serology among COVID-19 patients and vice versa ..
This can have serious consequences for with patient care and public health

If serologic tests are performed and antibody is detected, results should be interpreted with caution for the following reasons:

- It is currently unknown how long antibodies persist following infection
- It is currently unknown whether the presence of antibody confers protective immunity against future infection.

Assuming the test is reliable, serologic tests to identify recent or prior SARS-CoV-2 infection may be used to:

- Determine who may **be eligible to donate blood** to manufacture convalescent plasma.
- **Measure the immune response** in SARS-CoV-2 vaccine studies.
- Estimate the **proportion of the population exposed** to SARS-CoV-2. Lastly, serologic tests

should not be used to:

- Make decisions about the grouping of persons residing in or being admitted to congregate settings (e.g., schools, dormitories, correctional facilities), *or*
- Determine whether persons should return to the workplace.

Prevention and prophylaxis[1]

Tactics used to handle the virus:

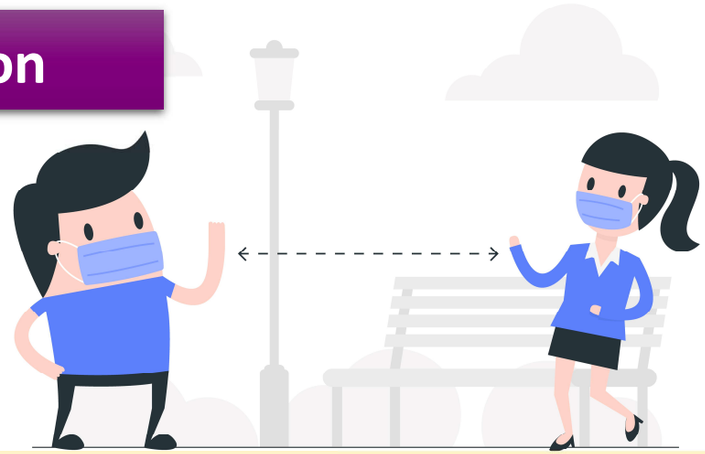
1. Measures to reduce Transmission. 2- Pre & post exposure prophylaxis measurements.

Covering coughs and sneezes

Wash Your hands frequently

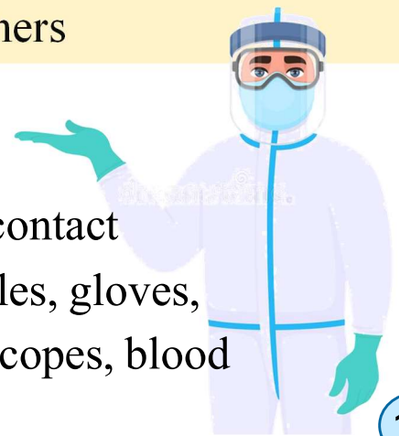
Measures used to reduce Transmission

face coverings may further reduce the spread of droplets

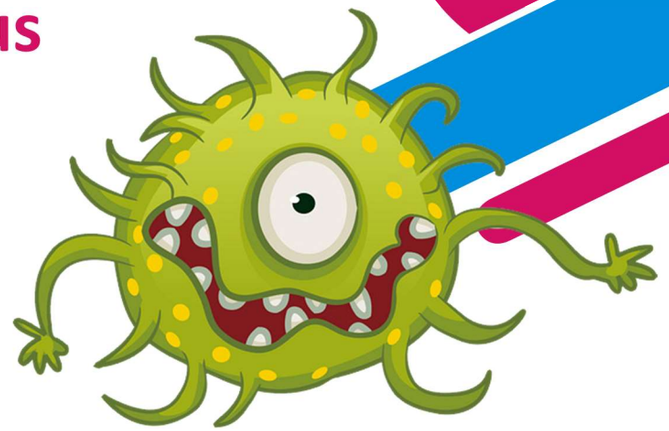


Maintaining a distance of 2 meters from others

Appropriate use of **personal protective equipment** for droplet and contact precautions along with eye protection (e.g., masks, face shields/goggles, gloves, gowns) and single-patient dedicated medical equipment (e.g., stethoscopes, blood pressure cuffs, thermometers).



Management of Patients with COVID and their status classification[5]



In general, adults with COVID-19 can be grouped into the following severity of illness categories, although the criteria in each category may overlap or vary across guidelines and clinical trials:

1. **Asymptomatic or Pre-symptomatic Infection**
2. **Mild Illness**
3. **Moderate Illness:**
4. **Severe Illness**
5. **Critical Illness**

At present, no known agent can prevent SARS-CoV-2 infection after exposure (i.e., as PEP).

But there are many agents under testing to be used in future aspects but further more testing to be approved

KDIC

Asymptomatic or Presymptomatic

- Individuals who test positive for SARS-CoV-2 by virologic testing using a molecular diagnostic (e.g., polymerase chain reaction) or antigen test, but have no symptoms.
- Persons who test positive for SARS-CoV-2 by molecular diagnostic or antigen testing and who are asymptomatic should self-isolate at home.
- If they **remain** asymptomatic, they can **discontinue isolation** 10 days after the date of their first positive SARS-CoV-2 test.
- Health care workers who test SARS-CoV-2 positive and are asymptomatic may obtain additional guidance from their occupational health service.

Mild Illness

- Individuals who have any of the various signs and symptoms of COVID 19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain) **without** shortness of breath, dyspnea, or abnormal chest imaging.
- Most mildly ill patients can be managed in an ambulatory setting or at home through telemedicine or remote visits.

KDIC

Moderate illness

Individuals who have evidence of lower respiratory disease by clinical assessment or imaging and a saturation of oxygen (SpO2) ≥94% on room air at sea level.
If bacterial pneumonia or sepsis is strongly suspected, administer empiric antibiotic treatment for community-acquired pneumonia, re-evaluate daily, and if there is no evidence of bacterial infection, de-escalate or stop antibiotics.

Severe illness

Individuals who have respiratory frequency >30 breaths per minute, SpO<94% on room air at sea level, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO /FiO) <300 mmHg, or lung infiltrates >50%.

Critical Illness

Severe cases of COVID-19 may be associated with :-
1-acute respiratory distress syndrome
2- septic shock that may represent virus-induced distributive shock
3-cardiac dysfunction
4-elevations in multiple inflammatory cytokines that provoke a cytokine storm
and/or exacerbation of underlying comorbidities.

In addition to pulmonary disease, patients with COVID-19 may also experience cardiac, hepatic, renal, and central nervous system disease.

As with any patient in the intensive care unit (ICU), successful clinical management of a patient with COVID-19 depends on attention to the primary process leading to the ICU admission, but also to other comorbidities and nosocomial complications.

The Egyptian MOH Protocol based on the most recent guidelines

The Egyptian MOH Protocol based on the most recent guidelines

It divides the protocol by the disease state

Mild case

Symptomatic case with lyphopenia or leucopenia with no radiological signs for pneumonia, age more than 60
And uncontrolled comorbidities, patient need to be isolated in hospital with treatment sd

- **Hydroxychloroquine**, 400mg twice in the 1st day then twice for 6 days
OR Ivermectin 6 mg (36mg on day 0-3-6)
OR Favipiravir 1600 mg twice in the 1st day then 600 mg twice daily.
- **Vitamin C** 1gm daily
- **Zinc** 50mg daily.
- **Acetyl cysteine** 200mg 3 times daily.
- **Lactoferrin** one sachet twice daily.

Moderate case

Patient has pneumonia manifestations on radiology associated with symptoms or lymphopenia

- **Lopinavir 250 mg or Ritonavir 50mg** *twice* per day
- **Ribavirin 400gm.**

Not recommended if symptoms continued for more than 7 days

Or

Hydroxychloroquine 400mg *twice* per day for the 1st day then 200mg twice per day for 9 days.

Anticoagulants as prophylactic

- **heparin** 5000 IU SQ 2 or 3 times per day

Or

Enoxaparin 40mg SQ once daily

If D-dimer is more than 1000 give the following as a therapeutic dose:

Heparin Infusion, IV Heparin Drip (**80 units/kg bolus**) then **continuous infusion of 18 units/kg/hr**

Or

Sub cutaneous initial 333 units/kg followed by 250 units/kg twice per day.

Enoxaparin: **1mg/kg sub cutaneous twice daily.**

- Steroids can be used if patient is dyspneic or CT Scan showed significant deterioration

Severe or crucially Ill case

If patients has SaO_2 less than 92, RR more than 30 or PaO_2/FiO_2 less than 200 despite oxygen therapy and chest radiology showing more than 50% Lesion or progressive lesion within 24hrs

Admit to ICU, Avoid hypoxia, prone awake or ventilated.

Anticoagulants:

- **Enoxaparin**: 1mg/kg and consider D-dimer level as a guide
- **Steroids** (methyl prednisolone) 1mg for no ventilated, 2mg for ventilated.
- **Tocilizumab** : 4-8 ,g/kg/dose max 2 doses early block cytokine storm if steroids failed

Antiviral drugs and antibiotics

- **Lopinavir** 200 mg or **Ritonavir** 50 mg (2 tab) twice per day
- **Ribavirin** 400mg twice per day
- **Interferon** beta b 1 + Azithromycin 500mg daily or doxycycline 200mg 1st day then 100 mg daily for 9 days
- •• If available, **remdesivir** 200mg in the 1st day, then 100mg daily for 9 days.

OR

- **Hydroxychloroquin**e if not contraindicated *400mg twice per day* in *the 1st day* then 100mg daily for 9 days
- **Lopinavir** 200 mg or **Ritonavir** 50 mg (2 tab) twice per day.
- **Azithromycin** 500mg daily or **doxycycline** *200mg 1st day* then 100 mg daily for 9 days.

Potential treatments for COVID-19[6]

According to the latest recognized Findings by the WHO, FDA & NIH

1. Potential Antiviral drugs
2. Potential Immunity enhancing and modifying drugs
3. Adjunctive Thereby

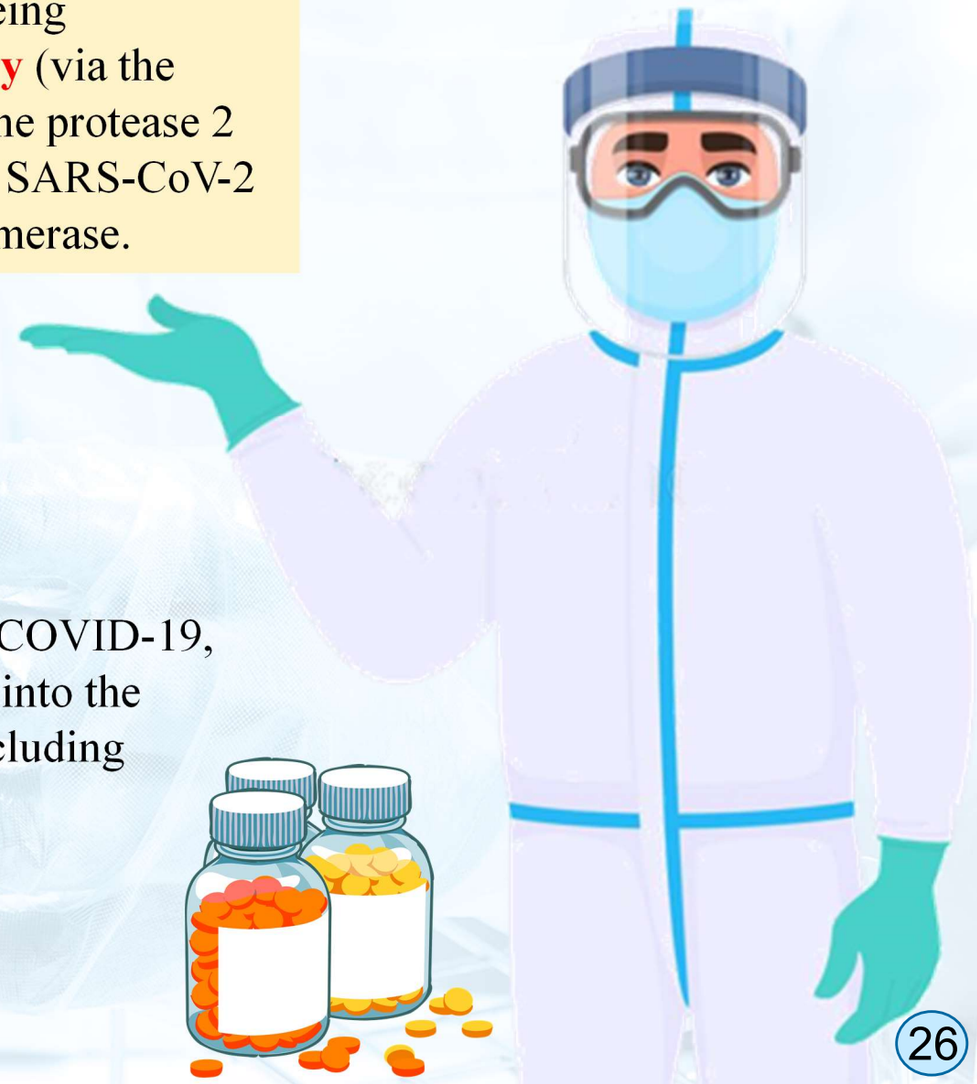
There are no FDA-approved drugs for the treatment of COVID-19.

Definitive clinical trial data are needed to identify safe and effective treatments for COVID-19

Potential Anti-viral Drugs

• Severe acute respiratory syndrome coronavirus 2(SARS-CoV-2) replication leads to many of the clinical manifestations of COVID-19. Antiviral therapies are being investigated for the treatment of COVID-19. These drugs **inhibit viral entry** (via the angiotensin-converting enzyme 2 [ACE2] receptor and transmembrane serine protease 2 [TMPRSS2]), viral membrane fusion and endocytosis, or the activity of the SARS-CoV-2 3-chymotrypsin-like protease (3CLpro) and the RNA-dependent RNA polymerase.

• Because viral replication may be particularly active early in the course of COVID-19, antiviral therapy may have the greatest impact before the illness progresses into the hyperinflammatory state that can characterize the later stages of disease, including critical illness.



Remdesivir[12]

• **Remdesivir is an intravenous (IV)** investigational nucleotide prodrug of an adenosine analog. Remdesivir binds to the viral RNA-dependent RNA polymerase, inhibiting viral replication through premature termination of RNA transcription. Remdesivir has been studied in several clinical trials for the treatment of COVID-19.

• The recommendations from the COVID-19 Treatment Guidelines Panel (the Panel) are based on the results of these studies.
The Panel recommends that remdesivir be prioritized for use in hospitalized patients with COVID-19 who require supplemental oxygen but who are not on high-flow oxygen, noninvasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) (BI)[15].

Drug Name	Remdesivir
Dosing	• **Hospitalized Adult and Pediatric Patients (Aged ≥12 Years and Weighing ≥40 kg**), RDV 200 mg IV over 30–120 minutes on Day 1, followed by RDV 100 mg IV on Day 2 through Day 5. • **For Mechanically Ventilated Patients and/or Patients on ECMO**: RDV 200 mg IV over 30–120 minutes on Day 1, followed by RDV 100 mg IV on Day 2 through Day 10. • **Hospitalized Pediatric Patients Weighing 3.5 kg to <40 kg or Aged <12 Years and Weighing ≥3.5 kg**: RDV 5 mg/kg IV over 30–120 minutes on Day 1, followed by RDV 2.5 mg/kg once daily starting on Day 2, •**For patients who are not mechanically ventilated and/or on ECMO, the recommended treatment duration is 5 days**
Monitoring Parameters	• Infusion reactions, Renal function, hepatic function, and prothrombin time.
Adverse Effects	• Gastrointestinal symptoms (e.g., nausea, vomiting), elevated transaminase levels, and an increase in prothrombin time.
Drug-Drug Interactions	• Clinical drug-drug interaction studies of remdesivir have not been conducted. Remdesivir levels are unlikely to be substantially altered by cytochrome P450 (CYP) 2C8, CYP2D6, or CYP3A4 enzymes, or by P-glycoprotein (P-gp) or organic anion-transporting polypeptide (OATP) drug transporters.
Considerations in Pregnancy	• Use remdesivir in pregnant patients only when the potential benefit justifies the potential risk to the mother and the fetus. • The safety and effectiveness of remdesivir for treatment of COVID-19 have not been evaluated in pregnant patients.
Consideration in children	• The safety and effectiveness of remdesivir for treatment of COVID-19 have not been evaluated in pediatric patients.
Consideration In Kidney patients	**Because the remdesivir formulation contains renally cleared sulfobutylether-beta-cyclodextrin sodium, patients with an eGFR of <50 mL/min are excluded from some clinical trials (some trials have an eGFR cutoff of <30 mL/min).**

Chloroquine or Hydroxychloroquine[6,7]

Chloroquine is an **antimalarial drug** that was developed in 1934. Hydroxychloroquine, an analogue of chloroquine, was developed in 1946 and is used to treat autoimmune diseases, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis. In general, hydroxychloroquine has fewer and less severe toxicities (including less propensity to prolong the QTc interval) and fewer drug-drug interactions than chloroquine

The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of **chloroquine** or **hydroxychloroquine** for the treatment of COVID-19, except in a clinical trial **(AII)**. – has been stopped

The Panel **recommends against** the use of **high-dose chloroquine** (600 mg twice daily for 10 days) for the treatment of COVID-19 **(AI)** [15].

The safety and efficacy of chloroquine and hydroxychloroquine have been evaluated in small randomized clinical trials, case series, and observational studies

Both chloroquine and hydroxychloroquine have immunomodulatory effects.

- Both chloroquine and hydroxychloroquine increase the endosomal pH, inhibiting fusion of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the host cell membranes.4

Drug Name	Chloroquine or Hydroxychloroquine
Dosing	***HYDROXY-CHLOROQUINE SULFATE*:** 400 mg twice /day one then 400 mg daily for 5 days (OR) 400 mg twice /day one then 200 mg twice daily for four days (OR) 600 mg twice/day one then 400 mg daily for four days. ***CHLOROQUINE*:** **>50Kg Oral 1g(600mg base) once on day one** followed by **500mg(300mg base) once daily** for a total treatment duration of 4-7 days **N.B.** Each 250 of Chloroquine phosphate is equivalent to 150 mg of Chloroquine base
Monitoring Parameters	ECG ----- CBC ----- Hepatic Panel ----- Renal Function ----- K & Mg levels ----- Blood Glucose
Adverse Effects	• QTc prolongation, Torsade de Pointes, ventricular arrythmia, and cardiac deaths. • The risk of QTc prolongation is greater for chloroquine than for hydroxychloroquine.
Drug-Drug Interactions	• Chloroquine and hydroxychloroquine are moderate inhibitors of cytochrome P450 (CYP) 2D6, and these drugs are also P-glycoprotein (P-gp) inhibitors.
Considerations in Pregnancy	• Antirheumatic doses of chloroquine and hydroxychloroquine have been used safely in pregnant women with SLE. • Hydroxychloroquine has not been associated with adverse pregnancy outcomes in ≥300 human pregnancies with exposure to the drug. • A lower dose of chloroquine (500 mg once a week) is used for malaria prophylaxis in pregnancy. • No dosing changes are necessary for chloroquine or hydroxychloroquine during pregnancy.
Consideration in children	• Chloroquine and hydroxychloroquine have been used routinely in pediatric populations for the treatment and prevention of malaria and for rheumatologic conditions

Hydroxychloroquine Plus Azithromycin[9]

The COVID-19 Treatment Guidelines Panel **recommends against** using **Hydroxychloroquine plus azithromycin** for the treatment of COVID-19, except in a clinical trial **(AIII)** [15].

Rationale

The combination of hydroxychloroquine and azithromycin is associated with QTc prolongation in patients with COVID-19. Given the long half-lives of both azithromycin (up to 72 hours) and hydroxychloroquine (up to 40 days), caution is warranted even when the two drugs are used sequentially instead of concomitantly

Doses

AZM 500 mg PO once on Day 1, then 250 mg PO daily on Days 2–5

Adverse effects

Multiple reports demonstrate that concomitant use of hydroxychloroquine and azithromycin can prolong QTc; in an observational study, hydroxychloroquine plus azithromycin was associated with increased odds of cardiac arrest.

Lopinavir/Ritonavir and Other HIV Protease Inhibitors[10]

NDC 0074-6799-22
Kaletra®
(Lopinavir/Ritonavir)
Tablets
200 mg /50 mg
120 Tablets
ALERT: Find out about medicines that should NOT be taken with Kaletra®
Note to Pharmacist: Do not cover ALERT box with pharmacy label. Enclosure is provided with tear-off patient information.
Rx only
Abbott

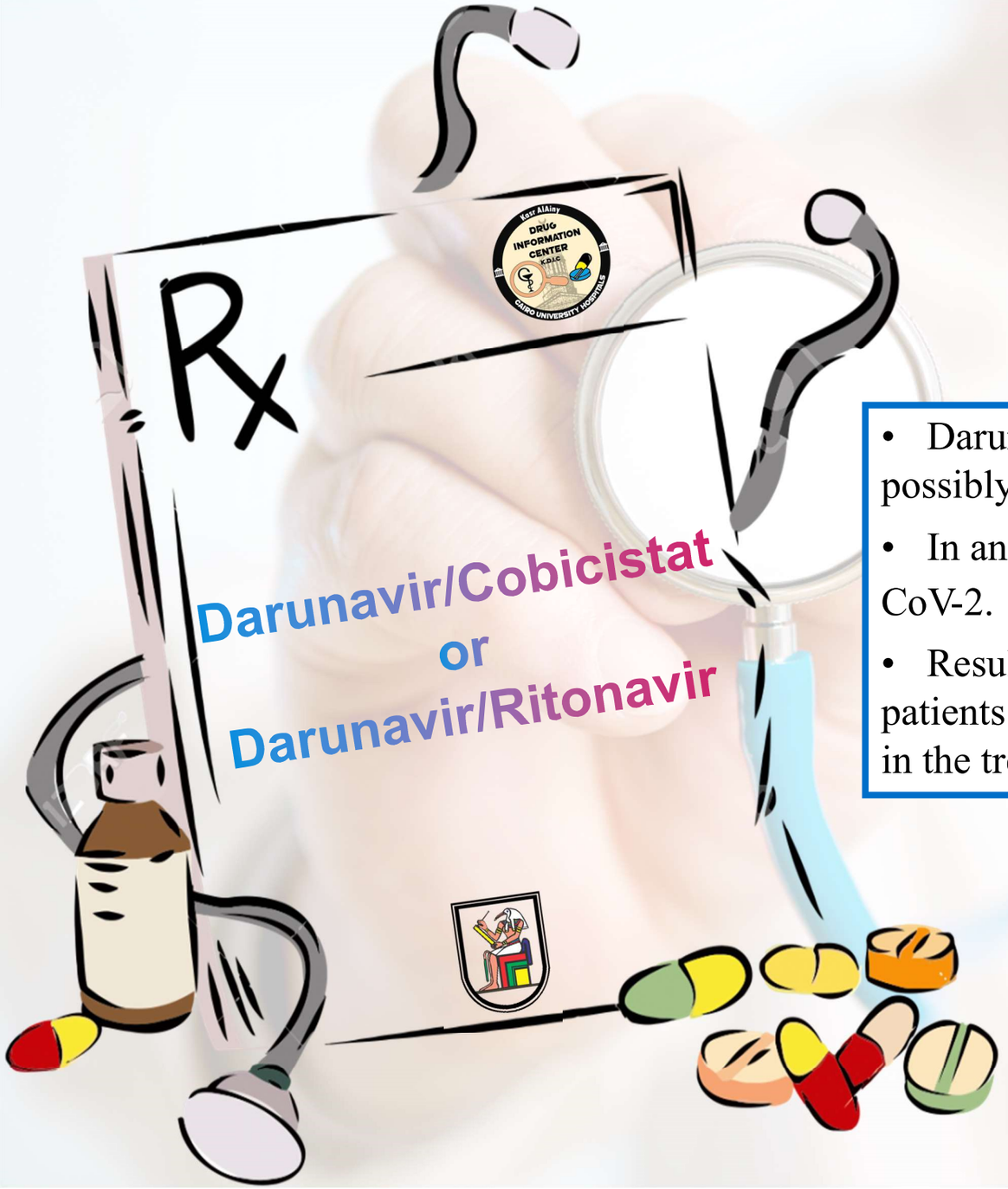
Replication of SARS-CoV-2 depends on the cleavage of polyproteins into an RNA-dependent RNA polymerase and a helicase.1 The enzymes responsible for this cleavage are two proteases:

3-chymotrypsin-like protease (3CLpro) and papain-like protease (PLpro).

- Lopinavir/ritonavir is an inhibitor of SARS-CoV 3CLpro *in vitro*, and this protease appears to be highly conserved in SARS-CoV-2.2,3
- Although lopinavir/ritonavir has *in vitro* activity against SARS-CoV, it is thought to have a poor selectivity index, indicating that higher than tolerable levels of the drug might be required to achieve meaningful inhibition *in vivo*.4
- Lopinavir is excreted in the gastrointestinal tract; therefore, coronavirus-infected enterocytes might be exposed to higher concentrations of the drug

The COVID-19 Treatment Guidelines Panel **recommends against** using **lopinavir/ritonavir (AI)** or other **HIV protease inhibitors (AIII)** for the treatment of COVID-19, except in a clinical trial [15].

Drug Name	Lopinavir/Ritonavir and Other HIV Protease Inhibitors
Dosing	**Adults:** • LPV/r 400 mg/100 mg PO twice daily for 10–14 days **Neonates Aged ≥14 Days with a PMA ≥42 Weeks and Children Aged <18 Years:** • LPV 300 mg/m2 plus RTV 75 mg/m2 (maximum: LPV/r 400 mg/100 mg per dose) PO twice daily for a total of 7 days.
Adverse Effects	Nausea, vomiting, diarrhea (common), QTc prolongation, Hepatotoxicity.
Drug-Drug Interactions	Lopinavir/ritonavir is a potent inhibitor of cytochrome P450 3A, and many medications that are metabolized by this enzyme may cause severe toxicity.
Considerations in Pregnancy	There is no evidence of human teratogenicity (can rule out a 1.5-fold increase in overall birth defects). Lopinavir has low placental transfer to the fetus. **Dosing:** Lopinavir/ritonavir oral solution contains 42.4% (volume/volume) alcohol and 15.3% (weight/volume) propylene glycol and **is not recommended** for use during pregnancy.
Considerations in Children	• Lopinavir/ritonavir is approved for the treatment of HIV in infants, children, and adolescents. • There are no data on the efficacy of using lopinavir/ritonavir to treat COVID-19 in pediatric patients



- Darunavir **inhibits the 3CLpro enzyme** of SARS-CoV-2 and possibly also inhibits the PLpro enzyme.
- In an *in vitro* study, darunavir did not show activity against SARS-CoV-2.
- Results from an unpublished Randomized controlled trial of 30 patients in China showed that darunavir/cobicistat was not effective in the treatment of COVID-19.

Potential Immunity enhancing and modifying drugs

• Given the hyperactive inflammatory effects of severe acute respiratory syndrome coronavirus 2 (SARS- CoV-2), agents that modulate the immune response are being explored as adjunctive treatments for the management of moderate to critical COVID-19.

• Some human blood-derived products are obtained from individuals who have recovered from SARS-CoV-2 infection (e.g., convalescent plasma, immunoglobulin products). Other agents in this group include therapeutics currently approved for the treatment of other immune and/or inflammatory syndromes.

• These agents include corticosteroids (e.g., glucocorticoids),[6] which as a class possess a broad array of mechanisms to abrogate systemic inflammation, and more targeted anti-inflammatory treatments such as interleukin inhibitors,[7,8] interferons,[9] kinase inhibitors,[10] and others

Recommendations

There are insufficient data for the COVID-19 Treatment Guidelines Panel[15] to recommend either for or against the use of the following blood-derived products for the treatment of COVID-19:

- **COVID-19 convalescent plasma**
- **Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) immunoglobulins**
- The Panel recommends against the use of the following blood-derived products for the treatment of COVID-19, except in a clinical trial:
- **Mesenchymal stem cells (AII)**
- **Non-SARS-CoV-2-specific intravenous immunoglobulins (IVIG) (AIII).**

Drug Name	COVID-19 convalescent plasma[13]
• Plasma from donors who have recovered from COVID-19 may contain antibodies to SARS-CoV-2 that may help suppress the virus and modify the inflammatory response. • On August 23, 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA)* for COVID-19 convalescent plasma for the treatment of hospitalized patients with COVID-19[78].	
Dosing	Single or multiple transfusions based on patient response
Adverse Effects	The risks associated with convalescent plasma transfusion include Transfusion related acute lung injury (TRALI) , Transfusion associated circulatory overload (TACO) and allergic transfusion reactions. Rare complications include the transmission of infectious pathogens and red cell alloimmunization. There is a theoretical risk of antibody-mediated enhancement of infection.
Considerations in Pregnancy	Several ongoing clinical trials evaluating COVID-19 convalescent plasma include pregnant women.
Considerations in Children	Clinical trials of COVID-19 convalescent plasma in children are ongoing.

SARS-CoV-2 Specific Immunoglobulins[14]

Concentrated antibody preparations derived from pooled plasma collected from individuals who have recovered from COVID-19 can be manufactured as SARS-CoV-2 immunoglobulin, which could potentially suppress the virus and modify the inflammatory response.

Drug Name	SARS-CoV-2 Specific Immunoglobulins
Dosing	• Varies by clinical trial
Considerations in Pregnancy	• Pathogen-specific immunoglobulins are used clinically during pregnancy to prevent varicella zoster virus (VZV) and rabies and have also been used in clinical trials of therapies for congenital CMV infection.
Considerations in Children	• Hyperimmunoglobulin has been used to treat several viral infections in children, including VZV, respiratory syncytial virus, and CMV; efficacy data on their use for other respiratory viruses is limited.

Non-SARS-CoV-2 Specific Immunoglobulins[15]

The COVID-19 Treatment Guidelines Panel recommends against the use of non-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-specific intravenous immunoglobulin (IVIG) for the treatment of COVID-19, except in a clinical trial (AIII).
This recommendation should not preclude the use of IVIG when otherwise indicated for the treatment of complications that arise during the course of COVID-19.

Drug Name	Non-SARS-CoV-2 Specific Immunoglobulins
Dosing	• Doses vary based on indication and formulation.
Considerations in Pregnancy	• IVIG is commonly used in pregnancy for other indications such as immune thrombocytopenia with an acceptable safety profile.
Considerations in Children	• IVIG has been widely used in children for the treatment of a number of conditions. including Kawasaki disease, and is generally safe. IVIG has been used in pediatric patients with COVID-19 and multiorgan inflammatory syndrome in children (MIS-C), especially those with a Kawasaki disease-like presentation, but the efficacy of IVIG in the management of MIS-C is still under investigation.

Mesenchymal Stem Cells[15]

• MSCs are multipotent adult stem cells that are present in most human tissues, including the umbilical cord.
MSCs can self-renew by dividing and can differentiate into multiple types of tissues, including osteoblasts, chondroblasts, adipocytes, hepatocytes[16 & 17].

• It is hypothesized that MSCs could reduce the acute lung injury and inhibit the cell-mediated inflammatory response induced by severe acute respiratory syndrome coronavirus2(SARS-COV-2)[18].

Furthermore**, MSCs lack the angiotensin-converting enzyme 2 receptor that SARS-COV-2 uses for viral entry into cells; therefore, MSCs are resistant to infection**[19].

• The COVID-19 Treatment Guidelines Panel **recommends against** the use of **mesenchymal stem cells** for the treatment of COVID-19, except in a clinical trial **(AII)**.

Drug Name	Mesenchymal Stem Cells
Dosing	Varies by clinical trial
Adverse Effects	Risks associated with MSC transfusion appear to be uncommon. The potential risks include failure of the cells to work as expected, potential for MSCs to multiply or change into inappropriate cell types, product contamination, growth of tumors, infections, thrombus formation, and administration site reactions.
Considerations in Pregnancy	There are insufficient data to assess the risk of MSC use during pregnancy.
Considerations in Children	There are insufficient data to assess the risk of MSC use during pregnancy.

Immunomodulators under Evaluation for the Treatment of COVID-19 [15]

- **Corticosteroids; Dexamethasone**
- **Interleukin-1 inhibitors** (e.g., anakinra)
- **Interleukin-6 inhibitors** (e.g., sarilumab, siltuximab, tocilizumab)
- **Interferons** (alfa or beta)
- **Bruton's tyrosine kinase inhibitors** (e.g., acalabrutinib, ibrutinib, zanubrutinib) and Janus kinase inhibitors (e.g.,baricitinib, ruxolitinib, tofacitinib) **(AIII).**

Corticosteroids[15]

The Panel recommends against using dexamethasone for the treatment of COVID-19 in patients who do not require supplemental oxygen (AI).

• If dexamethasone is not available, the Panel recommends using alternative glucocorticoids such as *prednisone, methylprednisolone, or hydrocortisone* (see Additional Considerations below for dosing recommendations) (AIII).

Additional Considerations

• Whether use of other corticosteroids (e.g., prednisone, methylprednisolone, hydrocortisone) for the treatment of COVID-19 provides the same benefit as dexamethasone is unclear. The total daily dose equivalencies to dexamethasone 6 mg (oral or intravenous [IV])[20,21] for these drugs are:

• **Prednisone 40 mg**

• **Methylprednisolone 32 mg**

• **Hydrocortisone 160 mg**

• Half-life, duration of action, and frequency of administration vary among corticosteroids.

• *Long-Acting Corticosteroid:* Dexamethasone; half-life: 36 to 72 hours, administer once daily.

• *Intermediate-Acting Corticosteroids:* Prednisone and methylprednisolone; half-life: 12 to 36 hours, administer once daily or in two divided doses daily.

• *Short-Acting Corticosteroid:* Hydrocortisone; half-life: 8 to 12 hours, administer in two to four divided doses daily

Drug Name	Dexamethasone [22-25]
Patients with severe COVID-19 can develop a systemic inflammatory response that can lead to lung injury and multisystem organ dysfunction. It has been proposed that the potent anti-inflammatory effects of corticosteroids might prevent or mitigate these deleterious effects.	
Dosing	Dexamethasone 6 mg daily IV or PO, for up to 10 days
Monitoring	Clinicians should closely monitor patients with COVID-19 who are receiving dexamethasone for adverse effects (e.g., hyperglycemia, secondary infections, psychiatric effects).
Adverse Effects	Prolonged use of systemic corticosteroids may increase the risk of reactivation of latent infections (e.g., hepatitis B virus, herpesviruses, strongyloidiasis, tuberculosis).
Drug-Drug Interaction	• Dexamethasone is a **moderate cytochrome P450** (CYP) 3A4 **inducer**. As such, it may reduce the concentration and potential efficacy of concomitant medications that are CYP3A4 substrates. • Clinicians should review a patient's medication regimens to assess potential interactions. • Coadministration of remdesivir and dexamethasone has not been formally studied, but a clinically significant pharmacokinetic interaction is not predicted.
Considerations in Pregnancy	• Several ongoing clinical trials evaluating the use of it in pregnant women treated from COVID-19.
Considerations in Children	The safety and effectiveness of dexamethasone or other corticosteroids for COVID-19 treatment have not been sufficiently evaluated in pediatric patients.

Drug Name	Interferons (Alfa, Beta)
Interferons, a family of cytokines with antiviral properties, have been suggested as a potential treatment for COVID-19 because of their *in vitro* and *in vivo* antiviral properties	
Dosing	• Peginterferon alfa-2a 180 mcg SQ once weekly for 2 weeks for MERS **IFN Alfa-2b:** *COVID-19 Clinical Trial* *Dosing:* Nebulized IFN alfa-2b 5 million units twice daily (no duration listed in the study) **IFN Beta-1a:**• 44 mcg SQ three times weekly10 for MERS • Duration for COVID-19 unknown [26] **IFN Beta-1b:**• 8 million units SQ, every other day, up to 7 days total for COVID-19 [27]
Adverse Effects	• The most frequent adverse effects of interferon-alfa include flu-like symptoms, nausea, fatigue, weight loss, hematological toxicities, elevated transaminases, and psychiatric problems (depression and suicidal ideation). Interferon-beta is better tolerated than interferon-alfa [28 & 29]
Drug-Drug Interaction	The most serious drug-drug interactions with interferons are the potential for added toxicity with other immunomodulators and chemotherapeutic agents [28 & 29]
Considerations in Pregnancy	Data from several large pregnancy registries did not demonstrate an association between exposure to interferon beta-1b preconception or during pregnancy and an increased risk of adverse birth outcomes (e.g., spontaneous abortion, congenital anomaly), and exposure did not influence birth weight, height, or head circumference [30-32]
Considerations in Children	There are limited data on the use of interferons for the treatment of respiratory viral infections in children.

Drug Name	Interleukin-1 Inhibitors
• Endogenous IL-1 is elevated in patients with COVID-19 and other conditions, such as severe CAR T-cell-mediated CRS. **• Case reports and case series have described favorable responses to anakinra in patients with these syndromes, including a survival benefit in patients with sepsis and reversal of cytokine storm after tocilizumab failure in adults with MAS.** [33,34]	
Dosing	• Standard adult dose is anakinra 100 mg SQ once daily • Has also been used IV • Duration unknown
Adverse Effects	• **Anakinra** was not associated with any significant safety concerns when used in clinical trials for the treatment of sepsis. [35-37] • Increased rates of infection were reported with prolonged **anakinra** use in combination with tumor necrosis factor-alpha blockade, but not with short-term use. [38]
Considerations in Pregnancy	There is limited evidence on which to base a recommendation in pregnancy, but unintentional first trimester exposure is unlikely to be harmful. [39]
Considerations in Children	**Anakinra** has been used extensively in the treatment of severely ill children with complications of rheumatologic conditions, including MAS. Pediatric data on the use of **anakinra** in ARDS/sepsis are limited.
Drug availability	Procuring **anakinra** may be a challenge at some hospitals in the United States. **Anakinra** is FDA- approved only for SQ injection.

Interleukin-6(IL-6) inhibitors (e.g., sarilumab, siltuximab, tocilizumab)[40]

- **IL-6 is a pleiotropic, pro-inflammatory cytokine** produced by a variety of cell types, **including** lymphocytes, monocytes, and fibroblasts. Infection by the related SARS-associated coronavirus induces a dose-dependent production of IL-6 from bronchial epithelial cells. [41]
- **Elevations in IL-6 levels may be an important mediator when severe systemic inflammatory responses occur** in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. COVID-19-associated systemic inflammation and hypoxic respiratory failure is associated with heightened cytokine release, as indicated by elevated blood levels of IL-6, C-reactive protein (CRP), D-dimer, and ferritin. [42-44]

Drug Name	Sarliumab [45]
Sarilumab is a recombinant humanized anti-interleukin-6 receptor (IL-6R) monoclonal antibody that is approved by the Food and Drug Administration (FDA) for use in patients with rheumatoid arthritis. It is available as a subcutaneous (SQ) formulation and is not approved for cytokine release syndrome (CRS).	
Dosing	• Sarilumab 400 mg IV (single dose) **Note:** The only FDA- approved sarilumab product is an SQ formulation.
Adverse Effects	• The primary lab abnormalities that have been reported with **sarilumab** treatment are transient and/ or reversible elevations in liver enzymes that appear to be dose dependent and rare occurrences of neutropenia and thrombocytopenia. Risk for serious infections (e.g., tuberculosis [TB], other bacterial pathogens) have been reported only in the context of long-term use of **sarilumab**.
Considerations in Pregnancy	• There are insufficient data to determine whether there is a drug-associated risk for major birth defects or miscarriage. • Monoclonal antibodies are actively transported across the placenta as pregnancy progresses (with greatest transfer during the third trimester) and may affect immune responses *in utero* in the exposed fetus.

Drug Name	Siltuximab [41]
Siltuximab is a recombinant human-mouse chimeric monoclonal antibody that binds IL-6 and that is approved by the FDA for use in patients with Castleman's disease. Siltuximab prevents the binding of IL-6 to both soluble and membrane-bound IL-6R, inhibiting IL-6 signaling. Siltuximab is dosed as an IV infusion.	
Dosing	• Siltuximab 11 mg/kg IV over 1 hour every 3 weeks for multicentric Castleman disease • Dose and duration for COVID-19 unknown
Adverse Effects	• The primary adverse effects (AEs) reported for **siltuximab** have been related to rash. Additional AEs, such as serious bacterial infections, have been reported only in the context of long-term dosing of **siltuximab** once every 3 weeks.
Considerations in Pregnancy	• There are insufficient data to determine whether there is a drug-associated risk for major birth defects or miscarriage. Monoclonal antibodies are transported across the placenta as pregnancy progresses (with greatest transfer during the third trimester) and may affect immune responses *in utero* in the exposed fetus.

Drug Name	Tocilizumab [46]
Tocilizumab is a recombinant humanized anti-IL-6R monoclonal antibody that is approved by the FDA for use in patients with rheumatologic disorders and CRS induced by chimeric antigen receptor T cell (CAR-T) therapy. **Tocilizumab** can be dosed for IV or SQ injection. For CRS, the IV formulation should be used. * It has been noted that the use of Tocilizumab in special ICU cases with COVID-19 might reduce mortality rate.*	
Dosing	• Tocilizumab 8 mg/kg IV once • Dose **should not exceed** tocilizumab 800 mg. • Dose may be repeated once, 12 hours later, if clinical symptoms worsen or show no improvement
Adverse Effects	• The primary laboratory abnormalities reported with **tocilizumab** treatment are elevated liver enzyme levels that appear to be dose dependent. • Neutropenia or thrombocytopenia are uncommon. • Additional AEs, such as risk for serious infections (e.g., TB, other bacterial pathogens), have been reported only in the context of continuous dosing of **tocilizumab**.
Considerations in Pregnancy	• There are insufficient data to determine whether there is a drug-associated risk for major birth defects or miscarriage. • Monoclonal antibodies are actively transported across the placenta as pregnancy progresses (with greatest transfer during the third trimester) and may affect immune responses *in utero* in the exposed fetus.
Considerations in Children	• In children, **tocilizumab** is frequently used for CRS following CAR-T therapy10 and it is occasionally used for MAS. Pediatric data for its use in ARDS/sepsis are limited.

Kinase Inhibitors: Bruton's Tyrosine Kinase Inhibitors and Janus Kinase Inhibitors

Bruton's tyrosine kinase (BTK) inhibitors: such as **acalabrutinib**, **ibrutinib**, and **zanubrutinib**.

Janus kinase (JAK) inhibitors: such as **baricitinib**, **ruxolitinib**, and **tofacitinib**.

BTK inhibitors and **JAK inhibitors** have broad immunosuppressive effects.

BTK inhibitors are licensed by the Food and Drug Administration (FDA) for the treatment of B-cell malignancies. [47]

BTK is a signaling molecule of the B-cell antigen receptor and cytokine receptor pathways. **BTK**'s role in signaling through the B-cell surface receptors results in activation of pathways necessary for B-cell trafficking, chemotaxis, and adhesion. [48]

JAK inhibitors are potent immunosuppressive agents that are FDA approved for the treatment of rheumatoid arthritis, psoriatic arthritis, polycythemia vera, myelofibrosis, ulcerative colitis, and graft- versus-host disease.

JAK inhibitors interfere with phosphorylation of signal transducer and activator of transcription (STAT) proteins. [49,50]

The kinase inhibitors are proposed as treatments for COVID-19 because they can prevent phosphorylation of key proteins involved in the signal transduction that leads to immune activation and inflammation (e.g., the cellular response to proinflammatory cytokines such as interleukin [IL]-6). [51]

Drug Name	Dose
Acalabrutinib [52]	**Dose for FDA-Approved Indications:** • Acalabrutinib 100 mg PO every 12 hours. • Dose and duration forCOVID-19 unknown.
Ibrutinib [53]	**Doses for FDA-Approved Indications:** • Ibrutinib 420 mg or 560 mg PO once daily. • Dose and duration for COVID-19 unknown.
Zanubrutinib [54]	**Dose for FDA-Approved Indications:** • Zanubrutinib 160 mg PO twice daily or 320 mg PO once daily. • Dose and duration for COVID-19 unknown.
Baricitinib [55,56]	**For Rheumatoid Arthritis:** • Baricitinib 2 mg PO once daily. **Doses for COVID-19 in Clinical Trials:** • Baricitinib 2 mg to 4 mg PO once daily for 7 to14 days.
Ruxolitinib [57,58,59]	• Doses for FDA-approved indications range from ruxolitinib 5 mg PO twice daily to 20 mg PO twice daily. • Doses in COVID-19 clinical trials range from ruxolitinib 5 mg PO twice daily to 20 mg PO twice daily, for 14 days.
Tofacitinib [60,61]	**Doses for FDA-Approved Indications:** • Tofacitinib 5 mg PO twice daily (rheumatoid and psoriatic arthritis). • Tofacitinib 10 mg PO twice daily (ulcerative colitis). • Dose and duration for COVID-19 unknown; A planned COVID-19 clinical trial will be evaluating 10 mg twice daily for 14 days.

Adverse Effects

• Most of the data on adverse effects of BTK and JAK inhibitors refer to chronic use of the agents. Adverse effects include infections (typically respiratory and urinary tract infections) and the reactivation of herpes viruses. Additional toxicities include myelosuppression and transaminase elevations. Hemorrhage and cardiac arrhythmia have occurred in patients who received BTK inhibitors. Thrombotic events and gastrointestinal perforation have occurred in patients who received JAK inhibitors.

Considerations in Pregnancy [62-64]

- **BTK inhibitors:** There is a paucity of data on human pregnancy and BTK inhibitor use.

In animal studies, in doses exceeding the therapeutic human dose, **acalabrutinib** and **ibrutinib** were associated with interference with embryofetal development.

Based on these data, **BTK inhibitors** may be associated with fetal malformations when use occurs during organogenesis.

The impact of use later in pregnancy is unknown. Risks of use should be balanced against potential benefits.

- **JAK inhibitors:** There is a paucity of data on the use of **JAK inhibitors** in pregnancy.

Fetal risk cannot be ruled out. Pregnancy registries provide some outcome data on **tofacitinib** used during pregnancy for other conditions (e.g., ulcerative colitis, rheumatoid arthritis, psoriasis).

Among the 33 cases reported, pregnancy outcomes were similar to those among the general pregnant population. Risks of use should be balanced against potential benefits.

Ivermectin

Guidelines Panel recommends against the use of ivermectin for the treatment of COVID-19, except in a clinical trial (AIII).

Ivermectin is a Food and Drug Administration (FDA)-approved antiparasitic drug that is used to treat several neglected tropical diseases, including onchocerciasis, helminthiases, and scabies.

Proposed Mechanism of Action and Rationale for Use in Patients With COVID-19

Ivermectin acts by inhibiting the host importin alpha/beta-1 nuclear transport proteins, which are part of a key intracellular transport process that viruses hijack to enhance infection by suppressing the host antiviral response.

Rational

Ivermectin has been shown to inhibit the replication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in cell cultures. However, pharmacokinetic and pharmacodynamic studies suggest that achieving the plasma concentrations necessary for the **antiviral efficacy detected *in vitro* would require administration of doses up to 100-fold higher than those approved for use in humans.**[77]

- Single dose of 200 μg/kg, with repeat dosing on Day 7 if the patient was still hospitalized (13 patients received a second dose
- All-cause mortality was lower among the patients in the ivermectin group than among patients in the usual care group (OR 0.27; P = 0.03). The mortality benefit appeared to be limited to the subgroup of patients with severe disease.
- There was no difference between the groups for the median length of hospital stay (7 days in both groups) or the proportion of mechanically ventilated patients who were successfully extubated (36% in the ivermectin group vs. 15% in the usual care group; P = 0.07).

The limitations of this retrospective analysis make it difficult to draw conclusions about the efficacy of
using ivermectin to treat patients with COVID-19.

Adjunctive Therapy Antithrombotic & coagulation Therapy in Patients with COVID-19

Infection with the novel coronavirus SARS-CoV-2 and the resulting syndrome coronavirus disease (COVID-19) has been associated with inflammation and a prothrombotic state, with increases in fibrin, fibrin degradation products, fibrinogen, and D-dimers

Managing Coagulopathy in Patients with COVID-19 [65]

1. **Selection of Anticoagulant or Antiplatelet Drugs for Patients with COVID-19.**
2. **Chronic Anticoagulant or Antiplatelet Therapy.**
3. **Patients with COVID-19 Who Are Managed as Outpatients.**
4. **Hospitalized Patients with COVID-19.**
5. **Patients with COVID-19 Who Are Discharged from the Hospital.**

Selection of Anticoagulant or Antiplatelet Drugs for Patients with COVID-19

Any time anticoagulant or antiplatelet therapy is being used, consideration must be given to potential drug-drug interactions with other concomitant drugs **(AIII)**.

Low molecular weight heparin or **unfractionated heparin** may be preferred in hospitalized, critically ill patients because of their shorter half-lives, ability to be administered intravenously or subcutaneously, and fewer drug-drug interactions compared with oral anticoagulants **(AIII)**.

Outpatients receiving **warfarin** who are unable to get international normalized ratio monitoring during isolation may be candidates for direct oral anticoagulant therapy.

Patients with mechanical heart valves, ventricular assist devices, valvular atrial fibrillation, or antiphospholipid antibody syndrome or patients who are lactating should continue treatment with warfarin therapy **(AIII)**

Chronic Anticoagulant or Antiplatelet Therapy

Patients with COVID-19 who are taking anticoagulant or antiplatelet therapy for underlying medical conditions should continue their treatment unless significant bleeding develops or other contraindications are present (AIII).

Patients with COVID-19 Who Are Managed as Outpatients

For non-hospitalized patients with COVID-19, anticoagulant or antiplatelet therapy should not be initiated for VTE prophylaxis or at therapeutic doses (AIII).

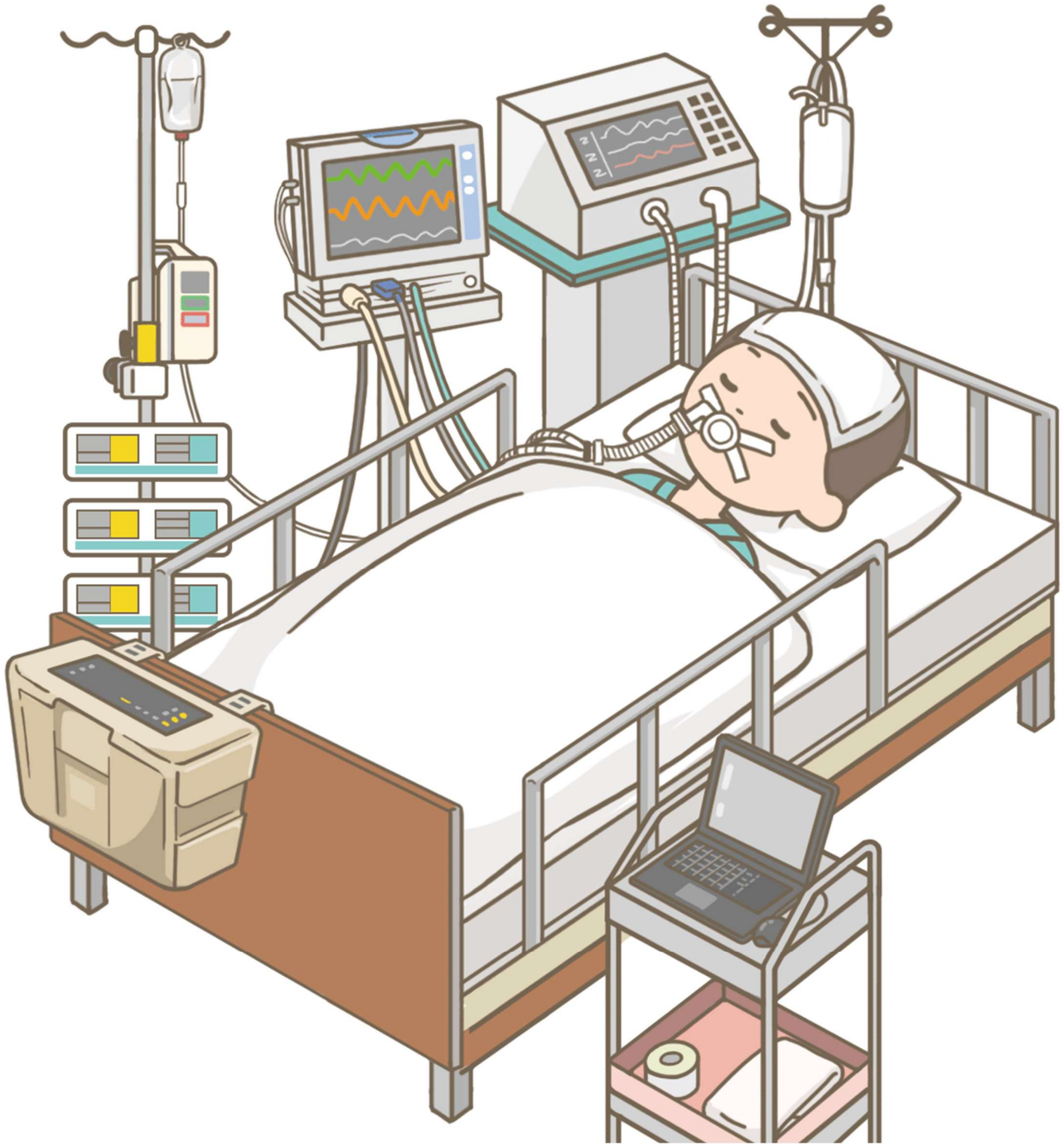
Summary of the recommendations for pharmacologic management of patients With COVID-19 According to the disease severity (NIH-October Update)

Disease Severity	Panel's recommendations
Not Hospitalized, or hospitalized but not require supplemental oxygen	• No specific antiviral or immunomodulatory theapy recommended, the panel recommends against the use of dexamethasone (AI)
Hospitalized and requires Supplemental oxygen (But doesn't require oxygen delivery through a high-flow device, non-invasive ventilation, invasive mechanical ventilator or ECMO)	• Remdesivir 200mg IV for 1 day, followed by 100mg IV once daily for 4 days or until hospital • discharge, whichever comes 1st (AII). Or • Remdesivir (dose and duration as mentioned) plus dexamethasone 6mg IV or PO for up to 10 days or until hospital discharge, whichever comes 1st. • If remdesivir can't be used, Dexamethasone may be used instead (BIII)
Hospitalized and requires oxygen delivery through a high-flow device or Non-Invasive Ventilation	• Dexamethasone Plus remdesivir at the doses and durations mentioned above (AIII) Or • Dexamethasone alone also at the dose and duration mentioned before (AI)
Hospitalized and requires invasive mechanical ventilation or ECMO	• Dexamethasone alone also at the dose and duration mentioned before (AI) Or • Dexamethasone Plus Remdesivir for patients who have recently been intubated at the does and durations mentioned before (CIII)

Additional Considerations

Remdesivir therapy may be extended to up to 10 days if no substantial clinical improvement is seen at Day 5.

- The combination of remdesivir and dexamethasone has not been studied in clinical trials; however, there are theoretical reasons for combining these drugs.
- The Panel recognizes there are theoretical reasons for adding dexamethasone to the drug regimen of patients who are currently receiving remdesivir but who are clinically deteriorating.
- If dexamethasone is not available, an alternative corticosteroid such as **prednisone**, **methylprednisolone**, or **hydrocortisone** can be used **(BIII)**.



COVID-19 Treatment Protocol

Hospitalized Patients with COVID-19

K.D.I.C
Cairo University Hospitals

Hospitalization Risk is increased by the following factors

- Older Age
- Black race
- Male sex
- Former smoking history
- Diabetes
- Hypertension
- Chronic lung disease
- Poor socioeconomic status
- Shortness of breath
- Diarrhea
- Certain medications (NSAIDS- Immunosuppressive medications)

Hospitalized Patients with COVID-19 [66,67]

For adults who are admitted to a hospital with COVID-19, VTE prophylaxis, unless contraindicated (e.g., a patient has active hemorrhage or severe thrombocytopenia), should be prescribed using the recommendations for patients who have been admitted to a hospital for other indications (**AIII**).

Anticoagulant or antiplatelet therapy should not be used to prevent arterial thrombosis outside of the standard of care for those without COVID-19 (**AIII**).

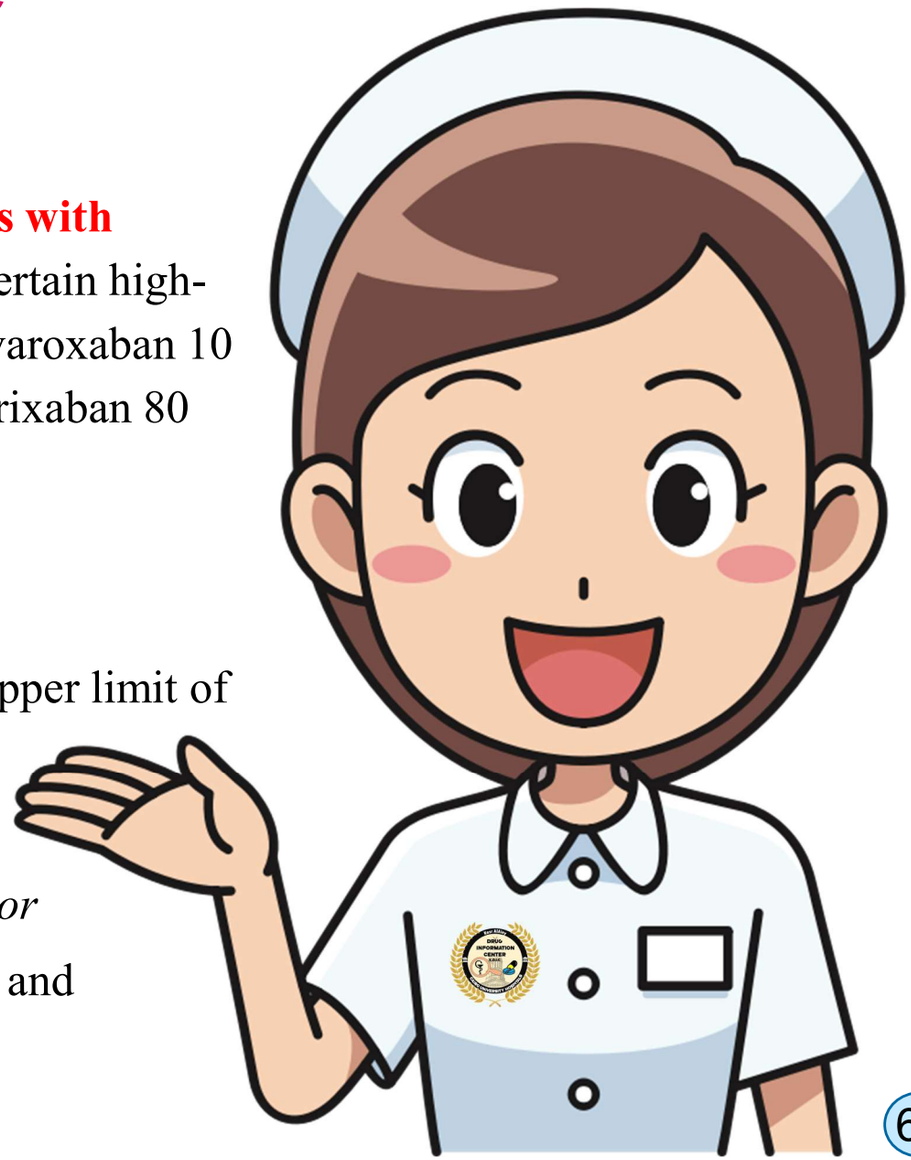
- Patients with COVID-19 who experience an incident thromboembolic event or who are highly suspected to have thromboembolic disease at a time when imaging is not possible should be managed with therapeutic doses of **anticoagulant therapy** as per the standard of care for patients without COVID-19 (**AIII**).
- Patients with COVID-19 who require extracorporeal membrane oxygenation or continuous renal replacement therapy or who have thrombosis of catheters or extracorporeal filters should be treated as per the standard institutional protocols for those without COVID-19 (**AIII**).

Patients with COVID-19 Who Are Discharged from the Hospital [68,69]

Routine post-discharge VTE prophylaxis is not recommended for patients with COVID-19 (AIII). However, the benefits of post-discharge prophylaxis for certain high-risk patients without COVID-19 led to the FDA approval of two regimens: rivaroxaban 10 mg daily for 31 to 39 days, and betrixaban 160 mg on Day 1, followed by betrixaban 80 mg once daily for 35 to 42 days.

Inclusion criteria for the trials that studied these regimens included:

- Modified IMPROVE-VTE score ≥4; *or*
- Modified IMPROVE-VTE score ≥2 and D-dimer level >2 times the upper limit of normal;16 *or*
- Age ≥75 years; *or*
- Age >60 years and D-dimer level >2 times the upper limit of normal; *or*
- Age 40 to 60 years, D-dimer level >2 times the upper limit of normal, and previous VTE event or cancer.



COVID-19 Treatment Protocol

Special Considerations for Pregnancy and Lactation

K.D.I.C
Cairo University Hospitals

Specific recommendations for pregnant women with COVID-19 include:

- If antithrombotic therapy is prescribed during pregnancy for another indication, this therapy should be continued if the patient receives a diagnosis of COVID-19 **(AIII)**.
- For pregnant patients admitted to the hospital with COVID-19, recommendations for VTE prophylaxis are the same as those for hospitalized nonpregnant patients **(AIII)**.
- Management of anticoagulation therapy during labor and delivery requires specialized care and planning and should be managed similarly in pregnant patients with COVID-19 as other conditions that require anticoagulation in pregnancy **(AIII)**.

Thrombolytic Therapy in Pregnancy

Due to the potential risk of maternal hemorrhage, during pregnancy, thrombolytic therapy should be reserved for acute pulmonary embolism with life-threatening hemodynamic instability regardless of whether a patient has COVID-19 **(AIII)**.[70]

Lactation

Unfractionated heparin, low molecular weight heparin, and warfarin do not accumulate in breast milk and do not induce an anticoagulant effect in the newborn; therefore, they can be used in breastfeeding women with or without COVID-19 who require VTE prophylaxis or treatment **(AIII)**.[71] In contrast, direct-acting oral anticoagulants are not routinely recommended due to the lack of safety data **(AIII)**.

COVID-19 Treatment Protocol

Special Considerations for People with HIV

K.D.I.C
Cairo University Hospitals

Management of COVID-19

• Recommendations for the triage, management, and treatment of COVID-19 in people with HIV are the same as those for the general population **(AIII)**.
• In people with advanced HIV and suspected or documented COVID-19, HIV-associated opportunistic infections (OIs) should also be considered in the differential diagnosis of febrile illness **(AIII)**.
• When starting treatment for COVID-19 in a patient with HIV, clinicians should pay careful attention to **potential drug-drug interactions** and **overlapping toxicities** among COVID-19 treatments, antiretroviral (ARV) medications, antimicrobial therapies, and other medications **(AIII)**.

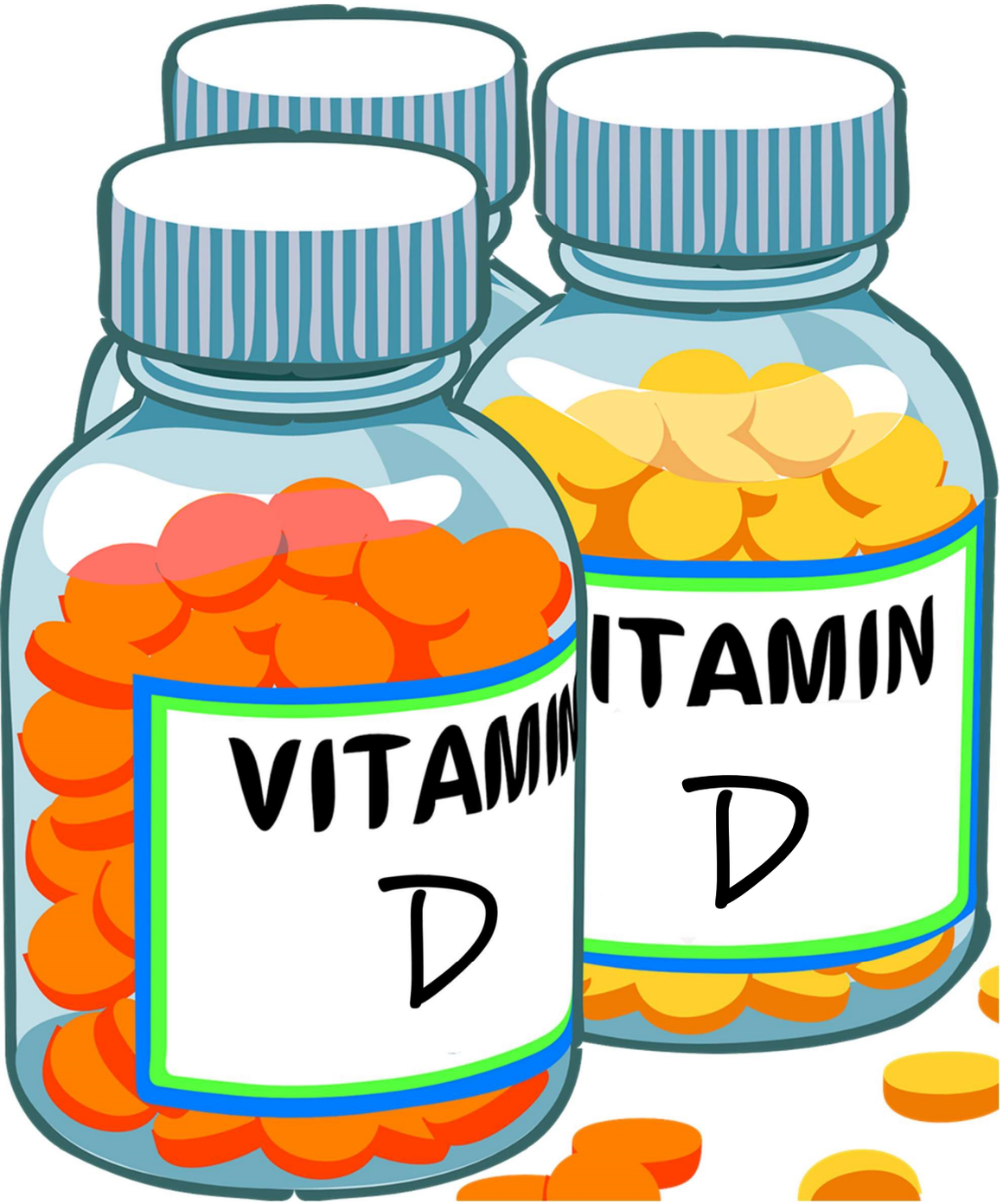
• People with HIV who develop COVID-19, including those who require hospitalization, **should continue their antiretroviral therapy** (ART) and OI prophylaxis whenever possible **(AIII)**.
• Clinicians treating COVID-19 in people with HIV should consult with an HIV specialist before adjusting or switching ARV medications **(AIII)**.
• An **ART regimen should not be switched or adjusted** (i.e., by adding ARVs to the regimen) for the purpose of **preventing or treating** SARS-CoV-2 infection **(AIII)**.
• For people who present with COVID-19 and a new diagnosis of HIV, clinicians should consult an HIV specialist to determine the optimal time to initiate ART (see text for more detailed discussion).

Vitamin C (ascorbic acid) is a water-soluble vitamin that is thought to have beneficial effects in patients with severe and critical illnesses. It is an antioxidant and free radical scavenger that has anti- inflammatory properties, influences cellular immunity and vascular integrity, and serves as a cofactor in the generation of endogenous catecholamines. [72, 73]

Other Considerations

It is worth noting that high circulating concentrations of vitamin C may affect the accuracy of point-of-care glucometers.

There are insufficient data for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of vitamin C for the treatment of COVID-19 in non-critically ill patients.



Vitamin D is critical for bone and mineral metabolism. Because the vitamin D receptor is expressed on immune cells such as B cells, T cells, and antigen-presenting cells, and because these cells can synthesize the active vitamin D metabolite, vitamin D also has the potential to modulate innate and adaptive immune responses. [74]

The role of vitamin D supplementation in the prevention or treatment of COVID-19 is not known. The rationale for using vitamin D is based largely on immunomodulatory effects that could potentially protect against COVID-19 infection or decrease the severity of illness. [75]

- There are **insufficient data to recommend either for or against the use of zinc for the treatment of COVID-19**.
- The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** using zinc supplementation above the recommended dietary allowance for the prevention of COVID-19, except in a clinical trial **(BIII)**[76].

Rationale

Increased intracellular zinc concentrations efficiently impair replication in a number of RNA viruses. [77]

Zinc has been shown to enhance cytotoxicity and induce apoptosis when used *in vitro* with a zinc ionophore (e.g., chloroquine). Chloroquine has also been shown to enhance intracellular zinc uptake *in vitro*. [78]

The relationship between zinc and COVID-19, including how zinc deficiency affects theseverity of COVID-19 and whether zinc supplements can improve clinical outcomes, is currently under investigation.

Considerations for Certain Concomitant Medications in Patients with COVID-19

Angiotensin-Converting Enzyme (ACE) Inhibitors and Angiotensin Receptor Blockers (ARBs)

- Persons with COVID-19 who are prescribed ACE inhibitors or ARBs for cardiovascular disease (or other indications) should continue these medications **(AIII)**.
- The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of ACE inhibitors or ARBs for the treatment of COVID-19, except in a clinical trial **(AIII)**[15].

HMG-CoA Reductase Inhibitors (Statins)

- Persons with COVID-19 who are prescribed statin therapy for the treatment or prevention of cardiovascular disease should continue these medications **(AIII)**.
- The Panel **recommends against** the use of statins for the treatment of COVID-19, except in a clinical trial **(AIII)**.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

- Persons with COVID-19 who are taking NSAIDs for a comorbid condition should continue therapy as previously directed by their physician **(AIII)**.
- The Panel recommends that there be no difference in the use of antipyretic strategies (e.g., with acetaminophen or NSAIDs) between patients with or without COVID-19 **(AIII)**.

Other Intensive Care Unit-Related Complications

Patients who are critically ill with COVID-19 are at risk for **nosocomial infections** and other complications of critical illness care, such as VAP, HAP, catheter-related bloodstream infections, and venous thromboembolism. When treating patients with COVID-19, clinicians also need to minimize the risk of conventional ICU complications in order to optimize the likelihood of a successful ICU outcome

Septic Shock and Cytokine Storm Due to COVID-19

Patients with COVID-19 may express high levels of an array of inflammatory cytokines, often in the setting of deteriorating hemodynamic or respiratory status. This is often **referred to as "cytokine release syndrome" or "cytokine storm,"** although these are imprecise terms. Intensivists need to consider the full differential diagnosis of shock **to exclude other treatable causes of shock** (e.g., bacterial sepsis due to pulmonary or extrapulmonary sources, hypovolemic shock due to a gastrointestinal hemorrhage that is unrelated to COVID-19, cardiac dysfunction related to COVID-19 or comorbid atherosclerotic disease, stress-related adrenal insufficiency).

Influenza and COVID-19

Diagnosis of Influenza and COVID-19 When Influenza Viruses and SARS-CoV-2 Are Cocirculating

- **Only testing can distinguish between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and influenza virus infections and identify SARS-CoV-2 and influenza virus coinfection.**

- **When SARS-CoV-2 and influenza viruses are cocirculating, the Panel recommends testing for both viruses in all hospitalized patients with acute respiratory illness (AIII).**

- **Testing in outpatients with acute respiratory illness if the results will change clinical management of the patient (BIII).**

http://https//www.ncbi.nlm.nih.gov/pubmed/32646801

http://https//www.ncbi.nlm.nih.gov/pubmed/32530499

Antiviral Treatment of Influenza When Influenza Viruses and SARS-CoV-2 Are Cocirculating

- The treatment of influenza is the same in all patients regardless of SARS-CoV-2 coinfection **(AIII)**.

- The Panel recommends that hospitalized patients be started on empiric treatment for influenza with **oseltamivir** as soon as possible without waiting for influenza testing results **(AII)**.
    - Antiviral treatment of influenza can be stopped when influenza has been ruled out by nucleic acid detection assay in upper respiratory tract specimens for non-intubated patients and in both upper and lower respiratory tract specimens for intubated patients.

Influenza Vaccination

Although data are lacking on influenza vaccination for persons with COVID-19, on the basis of practice for other acute respiratory infections, the Panel recommends that persons with COVID-19 should receive an inactivated influenza vaccine (BIII).

http://https//www.ncbi.nlm.nih.gov/pubmed/32720703

Emergency Use Authorization of Bamlanivimab for the Treatment of COVID-19

Nov. Update

Bamlanivimab is **a neutralizing monoclonal antibody** that targets the receptor-binding domain of the spike protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

The Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) to make bamlanivimab available for the treatment of nonhospitalized patients with mild to moderate COVID-19 who are at high risk for progressing to severe disease and/or hospitalization.

According to a published interim analysis of the trial, a total of 452 participants were randomized to receive one of three doses of bamlanivimab (700 mg, 2,800 mg, or 7,000 mg) or placebo.

https://www.fda.gov/media/143603/download.

High-Risk Criteria for Emergency Use Authorization of Bamlanivimab

- Individuals aged ≥12 years who have one of the following conditions:
  - BMI ≥35
  - Chronic kidney disease
  - Diabetes mellitus
  - Immunosuppressive disease
  - Currently receiving immunosuppressive treatment
- Individuals aged ≥65 years.
- Individuals aged ≥55 years who have:
  - Cardiovascular disease, *or*
  - Hypertension, *or*
  - Chronic obstructive pulmonary disease/other chronic respiratory disease.
- Individuals aged 12 to 17 years who have:
  - BMI ≥85th percentile for their age and gender based on the Center for Disease Control and Prevention growth charts; *or*
  - Sickle cell disease; *or*
  - Congenital or acquired heart disease; *or*
  - Neurodevelopmental disorders, for example, cerebral palsy; *or*
  - A medical-related technological dependence, for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19); *or*
  - Asthma or a reactive airway or other chronic respiratory disease that requires daily medication for control.

https://www.ncbi.nlm.nih.gov/pubmed/33113295.

Evidence strength

Rating of Recommendations:

A = Strong; B = Moderate; C = Optional

Rating of Evidence:

I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints

II = One or more well-designed, nonrandomized trials or observational cohort studies

III = Expert opinion

The Recommendation Panel

This panel is the National Institutes of Health (NIH) panel that recommends medical actions and interventions in COVID-19 patients based on the most recent Scientific studies, CDC Guidelines and the WHO recommendations.

References

as per the writing time

1- COVID-19 Treatment Guidelines – NIH - 30/7/2020.
2- https://www.cdc.gov/coronavirus/2019-ncov/hcp/infection-control.html.
3- https://www.cdc.gov/coronavirus/2019-nCoV/hcp/clinical-criteria.html.
4- https://www.ncbi.nlm.nih.gov/pubmed/32238024. Cited by 35 articles
5- https://www.ncbi.nlm.nih.gov/pubmed/32222812. Cited by 153 articles
6- https://www.ncbi.nlm.nih.gov/pubmed/32282022. Cited by 168 articles
7- https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/009768s037s045s047lbl.pdf.
8- https://www.medrxiv.org/content/10.1101/2020.04.16.20065920v2.
9- https://www.ncbi.nlm.nih.gov/pubmed/32289548. Cited by 72 articles
10- https://www.sciencedirect.com/science/article/pii/S2666634020300015.
11- https://www.ncbi.nlm.nih.gov/pubmed/32445440. Cited by 287 articles
12- https://www.ncbi.nlm.nih.gov/pubmed/32020029- Cited by 835 articles
13- https://www.ncbi.nlm.nih.gov/pubmed/25030060. Cited by 202 articles
14- https://pubmed.ncbi.nlm.nih.gov/32578948. Cited by 29 articles
15- https://www.covid19treatmentguidelines.nih.gov
16- https://www.ncbi.nlm.nih.gov/pubmed/28214990
17- https://www.ncbi.nlm.nih.gov/pubmed/297076267
18- https://www.ncb.nlm.nih.gov/pubmed/32292627
19- https://www.ncbi.nlm.nih.gov/pubmed/32257537
20- https://www.medrxiv.org/content/10.1101/2020.04.01.20048561v1.

For more references follow the NIH, CDC & WHO current guidelines for updated information of the current COVID-19 pandemic

References

as per the writing time

21- https://www.ncbi.nlm.gov/pubmed/32043986
22- https://www.ncbi.nlm.nih.gov/pubmed/32761166
23- https://www.ncbi.nlm.nih.gov/pubmed/32761993
24- https://www.cdc.gov/parasites/strongykoides/health_professionals/index.html
25- https://atjmh.org/content/journals/10.4269/atjmh.20-0699
26- https://www.ncbi.nlm.nih.gov/pubmed/32661006
27- https://www.ncbi.nlm.nih.gov/pubmed/32401715
28- https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/103132Orig1s51991b1.pdf
29- https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/1032Orig1s51991b1.pdf
30- https://www.ncbi.nlm.nih.gov/pubmed/21220368
31- https://www.ncbi.nlm.nih.gov/pubmed/32201504
32- https://www.ncbi.nlm.nih.gov/pubmed/31887199
33- https://www.ncbi.nlm.nih.gov/pubmed/26584195
34- https://www.ncbi.nlm.nih.gov/pubmed/32267081
35- https://www.ncbi.nlm.nih.gov/pubmed/8196140
36- https://www.ncbi.nlm.nih.gov/pubmed/8124953
37- https://www.ncbi.nlm.nih.gov/pubmed/9233735
38- https://www.ncbi.nlm.nih.gov/pubmed/29447987
39- https://www.ncbi.nlm.nih.gov/pubmed/26750125

References

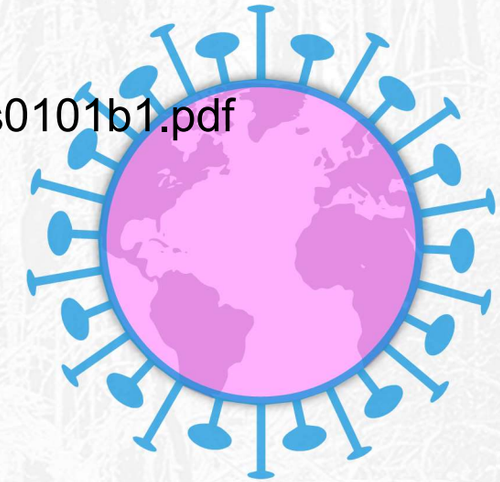
as per the writing time

40- https://www.medrxiv.org/content/10.1101/2020.04.01.20048561v
41- https://www.ncbi.nlm.nih.gov/pubmed/25684767
42- https://www.ncbi.nlm.nih.gov/pubmed/32171076
43- https://www.ncbi.nlm.nih.gov/pubmed/31986264
44- https://www.ncbi.nlm.nih.gov/pubmed/32176772
45- https://www.sanofi.com/en/media-room/press-releases/2020/2020-07-02-22-30-00
46- https://www.ncbi.nlm.nih.gov/pubmed/29622697
47- https://www.ncbi.nlm.nih.gov/pubmed/25669675
48- https://www.ncbi.nlm.nih.gov/pubmed/26582643
49- https://www.ncbi.nlm.nih.gov/pubmed/25057888
50- https://www.ncbi.nlm.nih.gov/pubmed/30109213
51- https://www.ncbi.nlm.nih.gov/pubmed/32222466
52- https://www.ncbi.nlm.nih.gov/32503877
53- https://www.ncbi.nlm.nih.gov/32302379
54- https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/213217s0001b1.pdf
55- https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/207924s0011b1.pdf
56- https://www.ncbi.nlm.nih.gov/pubmed/32333918
57- https://www.ncbi.nlm.nih.gov/pubmed/32113509
58- https://www.ncbi.nlm.nih.gov/pubmed/32470486

References

as per the writing time

59- https://www.ncbi.nlm.nih.gov/pubmed/32518419
60- https://www.ncbi.nlm.nih.gov/pubmed/24665995
61- https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/203214s024.208246s0101b1.pdf
62- https://www.ncbi.nlm.nih.gov/pubmed/27282428
63- https://www.ncbi.nlm.nih.gov/pubmed/29982686
64- https://www.ncbi.nlm.nih.gov/pubmed/32359679
65- https://www.hematology.org/covid-19/covid-19-and-vte-anticoagulation
66- https://www.ncbi.nlm.nih.gov/pubmed/32220112
67- https://www.ncbi.nlm.nih.gov/pubmed/28963294
68- https://www.ncbi.nlm.nih.gov/pubmed/32190813
69- https://www.ncbi.nlm.nih.gov/pubmed/2732649
70- https://www.ncbi.nlm.nih.gov/pubmed/30482767
71- https://www.ncbi.nlm.nih.gov/pubmed/29939933
72- https://www.ncbi.nlm.nih.gov/pubmed/21079686
73- https://www.ncbi.nlm.nih.gov/pubmed/25271834
74- https://www.ncbi.nlm.nih.gov/pubmed/212527855
75- https://www.clinicaltrials.gov
76- https://www.medrxiv.org/content/10.1101/2020/05.02.20080036v1
77- https://www.ncbi.nlm.nih.gov/pubmed/32251768.
78- https://www.fda.gov/media/141477/download



Thank You, this document is subjected to change, Updates will be reviewed and added

References are included